February 5, 2009

Dr. Barbara Shane, Executive Secretary
National Toxicology Program
Board of Scientific Counselors
NIEHS
P.O. Box 12233, MD A3-01
Research Triangle Park
North Carolina 27709

Dear Dr. Shane,

The NTP's Draft Substance Profile for styrene indicates that the evidence of the carcinogenicity of styrene in humans is limited. Contributing to this uncertainty are important gaps and inconsistencies in the epidemiologic information pertaining to styrene and cancer in humans, including the absence of convincing exposure-response data and variability among studies in the forms of cancer reported to be associated with styrene. The Draft's discussion of these issues is unclear in several instances.

The Draft notes that the most informative epidemiologic information on styrene and cancer in humans comes from studies of workers in the reinforced plastics industry and in the styrene-butadiene synthetic rubber industry. In describing this research, the Draft indicates that Kogevinas et al. (Scand J Work Environ Health 1994;20:251-261) observed that average exposure to styrene, but not cumulative exposure, was associated with lymphoma among workers in the European reinforced plastics industry. In discussing possible reasons for this inconsistency, the Draft states, "analyses of cumulative exposure are limited by the control for duration of exposure, which is correlated with cumulative exposure and thus may represent over-control"; and, "measures of intensity of exposure...may be more informative for evaluating risks in populations with a high-percentage of short-term workers than cumulative exposure." These possible explanations are not compelling. Kogevinas et al. (1994) used a standard approach to compute cumulative exposure and did not, as implied by the Draft, additionally control for duration of exposure in analyzing the relation between cumulative exposure to styrene and lymphoma. The Draft does not offer a biologic, mechanistic or methodological reason for its claim that average intensity of exposure styrene is a better measure than cumulative exposure. The high amount of random variability in the exposure-response data analyzed by Kogevinas et al. (1994) could easily explain their different results for cumulative exposure and average intensity of exposure. In the presence of such statistical imprecision, a firm conclusion about the existence of an exposure-response trend is unwarranted.

In discussing the results pertaining to leukemia in the study of Danish reinforced plastics workers, the Draft states, "Higher risks were ... found among workers with shorter duration of exposure (< 1 year) than longer duration of exposure." In fact, there was *no* increased risk of leukemia among workers with longer duration of exposure (i.e., those employed for at least one year), either in the group with <10 years since starting employment or in the group with at least 10 years since starting employment. The group with at least one year of employment and at least 10 years since starting employment also did not have any excess of non-Hodgkin lymphoma. The Draft states that other information cited by Kolstad et al. (Scand J Work Environ Health 1994;20:272-273) "suggested that many of those classified as short-term workers were long-term workers." However, the Draft does not provide a quantitative rationale for assuming that such misclassification could explain the null results for longer term workers.

Interpretation of research on styrene and cancer among workers in the styrene-butadiene synthetic rubber industry is hampered by the high correlation between exposure to styrene and butadiene, a recognized cause of leukemia. In our research on workers in this industry, we observed correlation coefficients for cumulative exposure styrene and butadiene of 0.79 among all subjects and 0.87 among workers with leukemia (Delzell et al., Res Rep Health Eff Inst, no.132:1-63, 2006). A further problem complicating the comparison of data from studies of the styrene-butadiene synthetic rubber industry with data from the reinforced plastics industry is the fact that styrene exposures were much lower in the styrene-butadiene synthetic rubber industry than in the reinforced plastics industry: 89% of the person-time of synthetic rubber industry workers in our study was contributed to styrene cumulative exposure categories of <61.1 ppm-years (Delzell et al., 2006), equivalent to the lowest styrene cumulative exposure category (60 ppm-years) analyzed by Kogevinas et al. (1994).

In our regression analyses of styrene-butadiene synthetic rubber industry workers, we observed a statistically non-significant relation between cumulative exposure to styrene and NHL and statistically significantly elevated rates of NHL/chronic lymphocytic leukemia (CLL) among workers with "highest" styrene cumulative exposure (61.1 or more ppm-years) (Delzell et al., 2006). In addition, a high number of tasks entailing exposure to estimated styrene concentrations of 50 or more ppm (but not styrene ppm-years) was associated with all leukemia combined. Residual confounding by butadiene, especially of associations seen for styrene and NHL/CLL and all leukemia, and statistical problems stemming from the inclusion of both styrene and butadiene, highly correlated variables, in regression models cannot be ruled out as explanations of these results.

The available scientific evidence is not sufficient to conclude that styrene causes lymphoma, leukemia or other cancers. In particular, the lack of consistent, reasonably precise associations between estimated exposure to styrene and NHL or leukemia in the studies of reinforced plastics industry workers is an important shortfall of the evidence for the hypothesis that styrene causes these cancers. This shortfall is not overcome by data from studies of synthetic rubber industry workers, due to the potential for residual confounding by butadiene and the very low levels of styrene experienced by workers in the latter industry.

My past research on workers in the synthetic rubber industry has been supported by the International Institute of Synthetic Rubber Producers, the American Chemistry Council, the Health Effects Institute and the Styrene Information and Research Center.

Yours respectfully,

Redacted

Elizabeth Delzell, Sc.D.